REMARKS

Claim 92 has been canceled since, as the Examiner observed, it is a duplicate of claim 91 and was inadvertently included in the prior submission. Claims 98-104 have been canceled without prejudice to their being refiled in a continuing application in view of the Examiner's remarks in paragraph 1 of the above-identified Office Action in which the Examiner concluded that the claims other than claims 98-104 have been constructively elected by their original presentation for prosecution on the merits and, therefore, claims 98-104 are withdrawn from consideration as being directed to a non-elected invention.

Claim 95 is provisionally rejected under the judicially created doctrine of obviousness-type double-patenting as being unpatentable over claims 2-4 of co-pending application No. 10/080,016. Applicants understand the Examiner's position with regard to claim 95. Appropriate action (e.g., a timely-filed terminal disclaimer in compliance with 37 CFR § 1.321(c)) will be taken as required to overcome this rejection at such time as the Examiner indicates that there is allowable subject matter, but for the obvious-type double-patenting rejection.

Claims 22, 23, 25-36, 83-94 and 96-98 are rejected under 35 U.S.C. § 103(a) as being unpatentable over *Robinson et al.*, U.S. 6,071,539 (hereinafter "*Robinson*"). This rejection is respectfully traversed.

In support of the rejection, the Examiner sets forth a series of arguments beginning on page 6, first full paragraph, through page 7, line 6. In summary, the Examiner argues that *Robinson* teaches oral formulations, such as tablets, containing effervescent granules, a binder and a therapeutic agent. In particular, the Examiner argues that *Robinson* discloses at column 4, lines 53-55, that the pH of the environment (e.g., the mouth) can be controlled by controlling the relative ratio of

the acidic and alkaline agents of the effervescent granules. In particular, the Examiner states that the ratio of the acidic agent and the alkaline agent can be determined according to the pH required for dissolving an active ingredient included in a formulation. Specifically, the Examiner quotes from *Robinson* beginning at column 4, line 58, and continuing through column 6, line 4 (*sic* column 5, line 4):

> "When the solubility of the active ingredient increases at the acid side, the pH of the solution is lowered by adding the acidic agent in an amount more than equivalent to the alkaline agent. When the solubility of the active ingredient increases at the basic side, the pH of the solution is raised by adding the alkaline agent in an amount more than equivalent to the acidic agent. In either case, the pH near the acidic agent immediately after the dissolution is low, while the pH near an alkaline agent is high."

The Examiner concludes, "Thus, the alkaline and/or acidic agents of *Robinson et al.* will act not only as effervescent agents, but also as pH adjusting agents." The Examiner then recites ranges taught in *Robinson* as being within the scope of those presently claimed. The Examiner further notes that *Robinson* teaches that once the tablet is placed in the patient's mouth, it will completely disintegrate.

In paragraph No. 8 of the Office Action, the Examiner notes that while *Robinson* teaches the claimed range, it does not explicitly teach that the amount of the effervescent couple should be greater than the amount necessary for tablet disintegration as required by the instant claims. However, the Examiner further observes that *Robinson* teaches that the amount

of the effervescent agents, as well as the ratio of acidic agent to alkaline agent, can be selected in order to achieve the desired rate of effervescence, and further to achieve substantially complete disintegration of the tablet and a "positive organoleptic sensation to a patient." Thus, the Examiner concludes, the determination of optimal or workable amounts of effervescent agents by routine experimentation in order to achieve the aforementioned desired effects is obvious absent showing criticality of the claimed amount. The Examiner concludes, therefore, that one having ordinary skill in the art at the time the invention was made would have been "motivated to employ effervescent agents of *Robinson et al.* in the amount greater than the amount necessary for disintegration of the tablet to insure "substantially complete" disintegration of the tablet and, as the result, a "positive organoleptic sensation to a patient." This rejection is respectfully traversed.

To begin with, in order to fully understand how the present invention is distinguished from *Robinson*, it is necessary to point out the nature of the advance claimed in *Robinson*. Reference to the claims (as well as the specification) of *Robinson* shows that the invention is directed to an effervescent granule comprising a mixture of an acidic agent, an alkaline agent and a hot-melt extrudable binder in combination with an active agent. In particular, the advance disclosed in *Robinson* relates to the use of a suitable binder to permit hot-melt extrusion and formation of an effervescent granule. The compositional features to which the Examiner refers are related to properties described in *Robinson* as relating to disintegration, dissolution and the organoleptic sensation in the mouth. In particular, the discussion in *Robinson* beginning at column 4, line 53, and continuing through column 5, line 4, cited by the Examiner, is directed to improving the dissolution of an active ingredient. Nowhere in

the cited portion, or elsewhere in *Robinson*, is there any disclosure, recognition or understanding of adjusting the amount of effervescent couple or the pH in order to improve penetration of an active pharmaceutical agent across the oral mucosa, as in the present invention. This distinction is significant, as shown by the further disclosure in *Robinson* beginning at column 8, line 11, and continuing through line 13:

> "Upon disintegration of the tablet, the therapeutic compound, which itself can be particulate, is released and can be swallowed as a slurry or suspension."

In other words, the objective of *Robinson* is to produce, e.g., a tablet, such that when placed in the mouth, it substantially completely disintegrates, and the pH of the local environment of the active ingredient will be such that it will dissolve in connection with being swallowed by the patient. Importantly, there is no suggestion or teaching in *Robinson* that the active ingredient is intended to be transported across the oral mucosa during the time that the tablet is present in the mouth. In fact, the only reference in *Robinson* to the "therapeutic compound" refers to it as being "swallowed."

In contrast, the references in *Robinson* to the conditions in the mouth of the patient relate solely to the organoleptic effect produced by the use of the effervescent agent. In particular, at column 7, beginning at line 63, *Robinson* teaches that the patient should be able to perceive a distinct sensation of "fizzing" or bubbling as the tablet disintegrates in the mouth. It is with regard to this sensation that the amount of effervescent couple is described by *Robinson*. As is well-known in the art, the term "organoleptic" refers to "stimulating any of the organs of sensation or susceptible to a sensory stimulus." (The Examiner's attention is invited to a

copy of the relevant page of "Stedman's Medical Dictionary" attached to this response.)

The extrapolation by the Examiner of the discussions in *Robinson* relating to effervescence, disintegration and a positive organoleptic sensation in order to reach Applicants' claims is nowhere to be found in the reference. The motivation to modify the amount of effervescent couple in combination with the pH adjusting substance as in the present claims in order to achieve an improved transport of the active ingredient across the oral mucosa is totally absent in *Robinson*. In particular, there is nothing in *Robinson* to suggest that the amount of effervescent couple required for substantially complete disintegration of the tablet and a positive organoleptic sensation to a patient is anything more than that required to just cause the tablet to disintegrate. Clearly, an effervescent couple, when activated in the mouth, will cause "fizzing" and thereby be perceived by the patient.

It is only the present invention that teaches that the amount of effervescent couple should be greater than that required for disintegration in order to achieve an improvement in transport of the active ingredient across the oral mucosa. It is only as a consequence of Applicants' teaching regarding this effect that the Examiner has extrapolated the teachings of *Robinson* in order to suggest that it is desirable to increase the amount of the effervescent couple and the pH of the composition in order to achieve the effect taught by Applicants; *Robinson* contains no such teaching or suggestion. It is clearly inappropriate for the Examiner to utilize Applicants' teaching in order to provide the motivation for modifying the limited disclosure of *Robinson*.

In summary, the Examiner has taken a reference, *Robinson*, directed to an invention for producing an effervescent granule, suitable for use with numerous "active ingredients"

(*see, e.g.*, column 2, lines 63-67) including herbicidal, industrial, agricultural, pesticidal, etc., as well as in pharmaceutical applications, but not directed to improving the delivery of a medicament, and particularly not across the oral mucosa. Consequently, it is not surprising that *Robinson* fails to teach the critical limitations of the present invention with regard to improving the transport of an active pharmaceutical ingredient across the oral mucosa by appropriate control of the amount of effervescent couple and the pH achieved by the composition. The most that *Robinson* teaches that is that their new effervescent granule is capable of achieving substantially complete disintegration of the tablet in which it is included as well as a pleasing, organoleptic sensation due to the "fizzing" of the effervescent couple. There can be no motivation in *Robinson* to modify the amounts of effervescent couple and pH adjusting substance in order to achieve an improvement in transport across the oral mucosa because *Robinson* itself is not directed to the transport of a pharmaceutical ingredient in the oral cavity. As stated above, its only reference to the consequence of a disintegrated tablet containing a therapeutic compound is that it can be "swallowed as a slurry or suspension." (column 8, line 13) Withdrawal of this rejection is respectfully requested.

Claim 95 is rejected under 35 U.S.C. § 103(a) as being unpatentable over *Robinson* as applied to claim 22 and further in view of *Norling et al.*, U.S. 5,958,458 (hereinafter "*Norling*").

The Examiner applies *Robinson* as explained above but notes that while broadly teaching analgesics, Robinson does not explicitly teach fentanyl of claim 95. The Examiner then states that *Norling* teaches that "fentanyl, among other analgesics, can be used in effervescent tablets including those of oral and buccal administration." Referring in *Norling* specifically to column 6, lines 23-24; column 12, lines 11-18; column 13, lines

30-31; and column 36, Example 13. The Examiner concludes that therefore it would have been obvious to one having ordinary skill in the art to modify the effervescent formulations of *Robinson* such that to employ fentanyl. Finally, it is stated that one having ordinary skill in the art would have been motivated to do this to obtain effervescent analgesic formulations as suggested by *Norling*. The Examiner concludes therefore that the invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made. This rejection is respectfully traversed.

The comments above with regard to *Robinson* are reiterated herein for the purposes of the rejection of claim 95. However, the Examiner's cursory treatment of *Norling* requires additional comment and analysis since the reference does not teach what the Examiner purports in the brief comments in paragraph 9 of the Office Action as noted above.

As a brief summary comment, and also as a prelude to a detailed analysis of *Norling*, it is noted that the claims and the teachings of the present application have been used as a guide in order to identify a reference such as *Norling* that includes, among much else, a reference to an effervescent material and a passing reference to the active ingredient fentanyl. In fact, it will be seen that *Norling* is a totally inappropriate reference with regard to the present invention.

To briefly review, *Norling* is directed to pharmaceutical multiple unit formulations in the form of small particle-size cores, particularly coated cores. Since the invention of the reference is applicable to various active drugs in combination with excipients, the document broadly and generically discloses various active drugs and excipients in compendium form. As stated in *Norling*, the objective was to develop a drug delivery system independent of solid or liquid dosage form (the latter being especially distinct from

Applicants' solid dosage form) and formulation to permit "drug delivery systems without regard to the administration route and/or the physical state of the drug delivery systems." (column 1, lines 32-34) In contrast, Applicants' administration route, the oral mucosa, is particularly important and specifically recited in the claims. This distinction emphasizes that, although the reference is directed to drug delivery forms, it should be viewed as directed to different technology, not relevant to the present claims. However, there is more that expressly distinguishes the reference, and Example 13 in particular, from the present invention.

Other than Example 13, the Examiner relies on column 6, lines 23-24. This portion of *Norling* does, indeed, recite that fentanyl is one of the active substances which can be used according to the disclosed invention. (It is also observed that the list of suitable active substances begins at column 6, line 23 and continues through column 8, line 13.) Consequently, the reference to fentanyl should be appreciated for what it is, a mere passing reference to one among a myriad of potentially active substances.

The next reference in *Norling* cited by the Examiner appears at column 12, lines 11-18. A quotation of the complete disclosure at this place is useful to illustrate that it adds little, if anything, to the argument presented by the Examiner:

> "A pharmaceutical formulations according to the invention may be adapted to administration via the oral, buccal, mucosal, nasal, rectal, vaginal, or topical route or to wounds. In other aspects, the present invention relates to solid dosage forms or liquid compositions comprising a pharmaceutical particulate formulation according to the invention. Such dosage

> forms or other suitable compositions (e.g., tablets, capsules, mixtures, sprays, etc.) according to the invention may be formulated according to conventional pharmaceutical practice, see, e.g., "Remington's Pharmaceutical Sciences" and "Encyclopedia of Pharmaceutical Technology", edited by Swarbrick, J. & J. C. Boylan, Marcel Dekker, Inc., New York, 1988."

It can be seen that this disclosure is nothing more than a generic disclosure of all routes of administration for various pharmaceutically active ingredients in various compositions. It does nothing to direct one to the specifically claimed subject matter and advance of the present invention.

The third specific reference in *Norling* relied on by the Examiner appears at column 13, lines 30-31. A complete quotation of the sentence that includes the two individual lines selected by the Examiner is as follows:

> "Formulations for oral use include solid dosage forms such as, e.g., powders, granules, sachets, tablets, capsules, effervescent tablets, chewable tablets, lozenges, immediate release tablets, and modified release tablets as well as fluid or liquid formulations such as, e.g., powders, dispersible powders or granules suitable for preparation of an aqueous suspension by addition of an aqueous medium, emulsions, dispersions and mixtures."

Again, it can be seen that the portion relied on by the Examiner is merely a generic dissertation of the various types of dosage forms suitable for use in pharmaceutical applications and does not teach or suggest specifically the use

of an effervescent tablet designed to achieve specific results such as in the present application. Clearly, Applicants do not assert that they are the first to have ever used effervescent compositions in a pharmaceutical application.

Finally, the Examiner relies on Example 13 as support for the obviousness rejection by combining this example of *Norling* with *Robinson*. However, it is necessary to closely examine Example 13 in order to understand its disclosure and its significance (more accurately, its insignificance) with regard to the present invention.

Example 13 is entitled "Preparation of Effervescent Tablets." However, the effervescent tablets of this example are not relevant or suitable for use in the present invention. Example 13 reports that tablets were prepared using "pellets from Example 6 coated with 50% w/w ethylcellulose." Referring back to Example 6, it is learned that individual pellets were prepared as described in Example 3, and in Example 6, the pellets were "coated with Surelease®" (which is a 25% w/w dispersion of ethylcellulose in water, cf. information under the heading "Materials")." The pellets of Example 3 included an inert carrier, a binder and theophylline as the active ingredient. For reference purposes, it is noted that "Surelease is a complete, optimally plasticized aqueous dispersion designed specifically for <u>modified release</u> and taste-masking applications. Using ethylcellulose as the rate controlling polymer, Surelease brings technological advances with dependable, reproducible <u>extended release profiles</u>..." (The Examiner's attention is invited to the literature of the manufacturer of the Surelease product, Colorcon, enclosed with this response.) (Emphasis added)

Clearly, the coating is used to form a pellet and to modify and extend the release profile of the active drug. The use of a coating to <u>extend</u> the release of a drug is inconsistent

and contrary to the present invention, wherein improved transport of the drug across the oral mucosa is the effect claimed. Evidence for this distinction is provided in *Norling* itself. As stated therein, "the dissolution of the tablets prepared was tested and compared with the dissolution of the pellets employed (denoted BDF 9)." (column 36, lines 53-56) Referring to the results reported in Table 11, column 36, relating to Example 13, the dissolution time of the pellets, i.e., the structure containing the active drug, shows that at 15 minutes only 4.2% was dissolved. In contrast, the inventors of *Norling* report that "the tablets disintegrated within 2 minutes." This suggests that the disintegrated tablet would be swallowed and the pellets containing the drug thereafter released in the stomach and/or digestive tract. Nothing further explains the discrepancy between the dissolution times for the tablets and the pellets as due to "partial rupture of the coated pellets during compression." (column 37, lines 14-16) Furthermore, it is noted that the dissolution test method employs 900 ml of a pH 7.5 phosphate buffered (aqueous) solution, i.e., a very dilute system containing a significantly greater volume of water or saliva than would be found in the mouth, and conducive to dissolution of the material under test in the reference. In contrast, the conditions in the mouth, the environment of the present invention, involve very small amounts of water present in saliva where transport across the oral mucosa is difficult, but where the objective is to increase the rate and extent of such transfer. The data reported in Example 13 of *Norling* demonstrate that the preparation and use of that extended release formulation resulted in, at best, dissolution in greater than 15 minutes and, more likely, in greater than 2 hours (as further indicated by the data).

Moreover, the results of *Norling* are inconsistent with the presently claimed compositions and methods that are directed

to enhancing the rate and/or extent of absorption of a medicament across the oral mucosa. Obviously, a patient is not expected to keep an effervescent tablet in their mouth for 15 minutes, and certainly not for 2 hours, when only 21.61% of the coated pellets are reported to have dissolved (but are not necessarily carried across the oral mucosa), even under the artificially advantageous conditions of the reference example.

Contrary to the Examiner's suggestion, it would not have been obvious to one having ordinary skill in the art to modify the effervescent formulations of *Robinson* so as to employ fentanyl on the basis of the teachings provided by *Norling*. In fact, relying on the teachings of *Norling*, one would have been motivated not to employ fentanyl in the effervescent composition of *Robinson* to arrive at Applicants' claimed compositions. However, recognizing that *Norling* discloses the use of coated cores containing an active pharmaceutical ingredient, perhaps including fentanyl, the combination of *Norling* with *Robinson* would result in a composition in which the effervescent granule facilitates the disintegration of the tablet and allows the coated core, remaining substantially undissolved, to be swallowed by the patient as described in *Robinson*. In that regard, *Robinson* and *Norling* are consistent with one another and contrary to the claims of the present invention. Withdrawal of the rejection of claim 95 is respectfully requested.

In conclusion, it is respectfully suggested that the Examiner has gathered together disparate, incidental disclosures of elements of Applicants' claims, using those claims as a guide, but without appropriate regard to the limitations of the claims or the objectives of the invention. In so doing, and after careful analysis of the references, it is clear that the references relied on by the Examiner are insufficient under the standards of 35 U.S.C. § 103(a), whether such references are

applied individually, as in the case of *Robinson*, or in view of one another, as with regard to claim 95.

As it is believed that all of the rejections set forth in the Official Action have been fully met, favorable reconsideration and allowance are earnestly solicited.

If, however, for any reason the Examiner does not believe that such action can be taken at this time, it is respectfully requested that she telephone Applicants' attorney at (908) 654-5000 in order to overcome any additional objections which she might have.

If there are any additional charges in connection with this requested amendment, the Examiner is authorized to charge Deposit Account No. 12-1095 therefor.

Dated: January 30, 2004

Respectfully submitted,

By _____

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functional structure or o. in the lower animals.
. of visi n, *organum* visus.
vomeronasal o., *organum* vomeronasale.
wandering o., floating or ptotic o.; an o. with loose attachments, permitting its displacement.
Weber's ., *utriculus* prostaticus.
.'s f Zuckerkandl, *corpora* paraaortica.

organa (ōr'gă-nă). Plural of organum.

organelle (or'gă-nel) [Mod. L. dim. of G. *organon,* organ]. Cell o.; organoid (3); one of the specialized parts of a protozoan or tissue cell; these subcellular units include mitochondria, the Golgi apparatus, nucleus and centrioles, granular and agranular endoplasmic reticulum, vacuoles, microsomes, lysosomes, plasma membrane, and certain fibrils, as well as plastids of plant cells.
cell o., organelle.
paired o.'s, rhoptries.

organic (ōr-gan'ik) [G. *organikos*] **1.** Relating to an organ. **2.** Relating to or formed by an organism. **3.** Organized; structural. **4.** See organic *compound.*

rganicism (ōr-gan'i-sizm). A theory which attributes all diseases, in particular, all mental disorders, to organic lesions.

rganicist (ōr-gan'i-sist). One who believes in, or subscribes to the views of, organicism.

organism (ōr'gă-nizm). Any living individual, whether plant or animal, considered as a whole.
calculated mean o. (CMO), a hypothetical o. whose characters are the means of both the positive and negative characters of the o.'s which belong to the same taxon as the CMO, as opposed to the hypothetical mean o.
fastidious o., a bacterial organism having complex nutritional requirements.
hypothetical mean o. (HMO), a hypothetical o. whose characters are the means of the positive characters of the organisms which belong to the same taxon as the HMO, as opposed to the calculated mean o.
pleuropneumonia-like o.'s (PPLO), the original name given to a group of bacteria which did not possess cell walls; these o.'s, isolated from man and other animals, soil, and sewage, are now assigned to the order Mycoplasmatales.

organization (ōr'gan-i-zā'shŭn). **1.** An arrangement of distinct but mutually dependent parts. **2.** The conversion of coagulated blood, exudate, or dead tissue into fibrous tissue.
pregenital o., in psychoanalysis, the o. or arrangement of the libido in the stages prior to that of genital primacy.

organize (ōr'gan-īz). To provide with, or to assume, a structure.

organizer (ōr'gan-ī-zer). H. Spemann's term originally applied to a group of cells on the dorsal lip of the blastopore inducing differentiation of cells in the embryo, and controlling growth and development of adjacent parts; now generally applied to any group of cells having such a controlling influence, the effects being brought about through the action of an evocator.
nucleolar o., nucleolar zone; the region of the satellites on the acrocentric chromosomes that is active in nucleolus formation.
primary o., the o. situated on the dorsal lip of the blastopore.
procentriole o., deuterosome.

organo- [G. *organon,* organ]. Combining form denoting organ or organic.

organoferric (ōr'gă-nō-fār'ik). Relating to an organic compound containing iron.

organogel (ōr-gan'ō-jel). A hydrogel with an organic liquid instead of water as the dispersion means.

organogenesis (ōr'gă-nō-jen'ĕ-sis) [organo- + G. *genesis,* origin]. Organogeny; formation of organs during development.

organ genetic, organogenic (ōr'gă-nō-jĕ-net'ik, -jen'ik). Relating to organogenesis.

organogeny (ōr-gan-oj'ĕ-nē). Organogenesis.

organography (ōr'gă-nog'ră-fē) [organo- + G. *graphē,* a writing]. A treatise on, or description of, the organs of the body.

organoid (ōr'gă-noyd) [organo- + G. *eidos,* resemblance]. **1.** Resembling in superficial appearance or in structure any of the organs or glands of the body. **2.** Composed of glandular or organic elements, and not of a single tissue; pertaining to certain neoplasms (*e.g.,* an adenoma) that contain cytologic and histologic elements arranged in a pattern that closely resembles or is virtually identical to a normal organ. See also histoid. **3.** Organelle.

organoleptic (ōr'gă-nō-lep'tik) [organo- + G. *lēptikos,* disposed to accept]. **1.** Stimulating any of the organs of sensation. **2.** Susceptible to a sensory stimulus.

organology (ōr-gă-nol'ō-jē) [organo- + G. *logos,* study]. Branch of science concerned with the anatomy, physiology, development, and functions of the various organs.

organoma (ōr-gă-nō'mă) [organo- + G. *-oma,* tumor]. A neoplasm that contains cytologic and histologic elements in such an arrangement that specific types of tissue, *e.g.,* thyroid glands, intestinal mucosa, ovarian stroma and follicles, may be identified in various parts. See also teratoma.

organomegaly (ōr'gă-nō-meg'ă-lē). Visceromegaly.

organomercurial (ōr-gan'ō-mer-kyū'rē-ăl). Any organic mercurial compound; *e.g.,* merbromin, thimerosal.

organometallic (ōr'gă-nō-me-tal'ik). Denoting an organic compound containing one or more metallic atoms in its structure.

organon, pl. organa (ōr'gă-non, ōr'gă-nă) [G. organ]. Organum.

organonomy (ōr-gă-non'ō-mē) [organo- + G. *nomos,* law]. The body of laws regulating the life processes of organized beings.

organonymy (ōr'gă-non'i-mē) [organo- + G. *onyma,* name]. The nomenclature of the organs of the body, as distinguished from toponymy.

organopathy (ōr-gă-nop'ă-thē) [organo- + G. *pathos,* suffering]. Any disease especially affecting one of the organs of the body.

organopexy, organopexia (ōr'gă-nō-pek-sē, -pek'sē-ă) [organo- + G. *pēxis,* fixation]. Fixation by suture or otherwise of a floating or ptotic organ.

organophilic (ōr'gă-nō-fil'ik). Pertaining to organophilicity.

organophilicity (ōr'gă-nō-fi-li'si-tē). Attraction of nonpolar substances (organic molecules) to each other.

organosol (ōr-gan'ō-sol). A hydrosol with an organic liquid instead of water as the dispersion means.

organotaxis (ōr'gă-nō-tak'sis) [organo- + G. *taxis,* orderly arrangement]. The tendency to migrate to a certain organ selectively.

organotherapy (ōr'gă-nō-thār'ă-pē). Treatment of disease by preparations made from animal organs; now frequently by synthetic preparations instead of extracts of a gland.

organotrophic (ōr'gă-nō-trof'ik) [organo- + G. *trophē,* nourishment]. Pertaining to the nourishment of an organ.

organotropic (ōr'gă-nō-trop'ik). Pertaining to or characterized by organotropism.

organotropism (ōr-gă-not'rō-pizm) [organo- + G. *tropē,* a turning]. Organotropy; the special affinity of particular drugs, pathogens, or metastatic tumors for particular organs or their component parts. *Cf.* parasitotropism.

organotropy (ōr-gă-not'rō-pē). Organotropism.

organ-specific. Denoting or pertaining to a serum produced by the injection of the cells f a certain organ or tissue that, when injected into another animal, destroys the cells of the corresponding organ.

organum, pl. rgana (ōr'gă-nŭm, ōr'gă-nă) [L. tool, instrument].

Stedman's
MEDICAL DICTIONARY

25th Edition

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Accurate indications, adverse reactions, and dosage schedules for drugs are provided in this book, but it is possible that they may change. The reader is urged to review the package information data of the manufacturers of the medications mentioned.

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SURELEASE®

AQUEOUS ETHYLCELLULOSE DISPERSION

Product Information

Product Specification

Formula No. E-7-7050

Surelease is a complete, optimally plasticized aqueous dispersion designed specifically for modified release and taste masking applications. Using ethylcellulose as the rate controlling polymer, Surelease brings technological advances with dependable, reproducible extended release profiles that are consistent from laboratory to pilot and production scale processes.

❑ Key Characteristics

- Aqueous dispersion
- Complete, optimally formulated system
- Easy to use and environmentally friendly
- Consistent and reproducible drug release profiles
- Regulatory acceptance in the United States, Europe and certain other regions.

❑ Applications

- Bead & Particle Coating:
  Fluid-bed coating is the usual technique used for coating of small particles.
- Matrix Granulation:
  Wet granulation binder for production of free flowing powder for compression into modified release tablets.
- Taste Mask Coating:
  Water insoluble coating providing highly effective taste mask.

❑ General Manufacturing Process Description

- Ethylcellulose is blended with Oleic Acid and Dibutly Sebecate, then extruded and melted. The molten plasticized ethylcellulose is then directly emulsified in ammoniated water in a high shear mixing device under pressure. Ammonium Oleate is formed in situ to stabilize and form the dispersion of plasticized ethylcellulose particles. Additional Purified Water is then added to achieve the final solids content. Colloidal Anhydrous Silica is then dispersed into the material to form the final product. (Reference: U.S Patents 4,123,403 and 4,502,888).

❑ Stability

- Surelease provides dependable modified release dissolution performance throughout its shelf life period.
- Some degradation of the Dibutyl Sebacate and Oleic Acid occurs during the manufacturing process. The extent of this degradation and identification/qualification of the specific degradants is currently under investigation.

❑ Packaging

- Surelease is supplied as a 25% w/w dispersion in tight-head polyethylene containers. Surelease is available in multiples of 10.0 kg weights.

❑ Shelf Life

- Surelease has a shelf life of 18 months from date of manufacture when properly stored.

❑ Recommended Storage Conditions

- Store in tightly sealed containers. Avoid exposure to high humidity and temperatures above 30° C (86° F).
  Keep from freezing

❑ **Specifications**

Description:	Off-white turbid liquid that dries to a clear film
Identification:	Conforms
Solids Content:	24.0 - 26.0%
Residue on Content:	1.6 - 1.95%
pH:	9.5 - 11.5

❑ **Quality Control Test Procedures**

Residue on Ignition:	USP<733> & Colorcon
pH:	USP<791>
Solids/Loss on Drying:	USP <731> & Colorcon
I.R. Identification:	USP <197K> & Colorcon

❑ **Performance Testing** — Each batch of Surelease is coated onto a drug substrate and tested for release rate to insure consistent, reliable performance

❑ **Component and Impurity Profile Testing** — Methods are under development to identify and monitor the quantitative levels of key components and impurities. (See Stability Section)

❑ **U.S Drug Master File Reference** — #9822 (11/5/92)

❑ **Regulatory Status of Raw Materials**

Ingredient	Compendial Reference
Purified Water:	USP, PhEur, JP
Ethylcellulose 20cP:	NF, PhEur, JPE, FCC, 21CFR 73.1, 73.1001, 172.868
Ammonium Hydroxide 28%:	NF, PhEur, FCC
Dibutyl Sebacate:	NF
Oleic Acid*:	NF, 21 CFR 172.860, Food Grade
Colloidal Anhydrous Silica:	21CFR 172.480

*Meets requirements of the EU-CPMP/BWP/1230/98

Colorcon®

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Locations	Telephone	Facsimile	Locations	Telephone	Facsimile
United States			*Asia/Pacific*		
Santa Ana, California	714-549-0631	714-549-4921	Singapore	65-438-0318	65-438-0178
Indianapolis,Indiana	317-545-6211	317-545-6218	Fuji-gun, Shizuoka, Japan	81-5-4465-2711	81-5-4465-2730
Humacao, Puerto Rico	787-852-3815	787-852-0030	Shanghai, China	86-21-5442-2222	86-21-5442-2229
			Mumbai, India	91-22-868-2537	91-22-868-4518
Europe			Seoul, Korea	82-2-2057-2713	82-2-2057-2179
Dartford, Kent, England	44-1322-293000	44-1322-627200			
Bougival, France	33-1-3082-1582	33-1-3082-7879	*Latin America*		
Idstein, Germany	49-6126-9961-0	49-6126-9961-11	Buenos Aires,Argentina	54-11-4552-1565	54-11-4552-5158
Gallarate, Italy	39-0331-776932	39-0331-776831	Cotia, Brasil	55-11-4612-4262	55-11-4612-3307
Budapest, Hungary	36-1-200-8000	36-1-200-8010	Bogota, Columbia	571-418-1202	571-418-1257
Istanbul, Turkey	90-216-465-0360	90-216-465-0361	Caracas, Venezuela	58-212-442-4819	58-212-442-8724
Barcelona, Spain	34-9-3589-3756	34-9-3589-3792	Santa Fe, Mexico	525-292-1611	525-292-1750

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